DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Administrative File, BLA STN 125555/0 Antihemophilic Factor VIII (Recombinant), Plasma/Albumin Free

From: Michael Vardon, OCBQ/DMPQ/MRB2

Through: Marion Michaelis, Branch Chief, CBER/OCBQ/DMPQ/MRB2

Cc: Jiahua Qian, Regulatory Project Manager, CBER/OBRR/IOD/RPM
Nancy Kirschbaum, PhD, Chemist, CBER/OBRR/DHRR/LH
Andrey Sarafanov, PhD, Chemist, CBER/OBRR//DHRR/LH

Subject: Addendum Review of the BLA submitted by Octapharma Pharmazeutika Produktionsges.m.b.H., License 1646, for the control of bleeding episodes and perioperative management in patients with hemophilia A

Due Date: June 5, 2015

REVIEW RECOMMENDATION

I recommend approval based on the review of the firm's responses and additional information submitted.

INSPECTION FOLLOW-UP

Per a teleconference on May 13, 2015, Octapharma was advised that their shipping validation studies were not complete and the manual visual inspection training procedure did not reflect routine production operations. I recommend the following items should be evaluated on the next inspection at Octapharma's Stockholm, Sweden facility:

- Confirm the ongoing shipping validation study for the 3 mL water-for-injection (WFI) diluent container shipped from (b) (4) is complete;
- Confirm the shipping study of the final product presentation includes air freight transportation to the US is complete.
- Confirm the firm has revised and improved their manual visual inspection training and qualification program to reflect routine operations.

Review Summary

Octapharma Pharmazeutika Produktionsges.m.b.H. (Octapharma) submitted a BLA under STN 125555/0 for licensure of Antihemophilic Factor (Recombinant), Nuwiq®, for the control and prevention of bleeding episodes and perioperative management in patients with hemophilia A. The BLA was submitted by Octapharma and received by CBER on June 5, 2014.

Antihemophilic Factor (Recombinant) is supplied as a lyophilized powder and is reconstituted with a single-dose solvent pre-filled syringe containing 2.5 mL of sterile water for injection before intravenous injection. There will be four nominal strengths: 250, 500, 1000, and 2000 international units/vial.

CBER performed a Pre-License Inspection (PLI) at the Octapharma AB facility in Stockholm, Sweden from October 21-24 and 27-28, 2014 to support the review of STN 125555/0. The Stockholm facility is used for the manufacture of the drug substance and drug product. The inspectional findings are documented in the Establishment Inspection Report (EIR).
The purpose of the BLA submission for Antihemophilic Factor (Recombinant) is to seek approval for a new Drug Substance (DS) and Drug Product (DP) manufacturing facility located at Elersvägen 40, 112 75, Stockholm, Sweden.

Please refer to my discipline review memo for a review of the BLA STN 125555/0 and Amendments STN 125555/0/5 and STN 125555/0/6. This review memo is addendum that covers Amendments STN 125555/0/19, STN 125555/0/23, STN 125555/0/32, STN 125555/0/38, STN 125555/039 and STN 125555/0/42.

As this is a recombinant product, this review was conducted under FDA's *Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-derived Product or a Monoclonal Antibody Product for In Vivo Use*. Under this guidance, limited information is required to be submitted regarding facility and equipment. As such, my review is based on this guidance document.

Review Narrative

Items Reviewed

- Amendments STN 125555/0/19, STN 125555/0/23, STN 125555/0/32, STN 125555/0/38, STN 125555/0/39 and STN 125555/0/42
- Teleconferences were held on April 13, 2015, April 30, 2015 and May 13, 2015

Review of Amendments STN 125555/0/19 and STN 125555/23 regarding information request sent January 15, 2015

The following review questions were communicated to the sponsor on January 15, 2015. On January 30, 2015, CBER received a partial responses from the sponsor in Amendment STN 125555/0/19. On February 27, 2015, CBER received the additional response information from

Octapharma in Amendment STN 125555/0/23. A summary of my review questions (in *Italics*), Octapharma's responses (in regular text) and my comments (in **bold**) are below:

1. *Confirm material produced from freeze dryer* (b) (4) *will not be distributed to US market since you decided not to perform the required validation actions and have scheduled to take this freeze dryer out of service by July 2015.*

Firm's Response
Octapharma confirmed that no material produced from freeze-dryer (b) (4) will be distributed to the US market.

Reviewer's Comments
This response is acceptable.

2. *Confirm the* (b) (4) *freeze dryer will no longer be used for any other US marketed products.*

Firm's Response
Octapharma confirmed the (b) (4) freeze-dryer will no longer be used for any other US marketed products.

Reviewer's Comments
This response is acceptable.

Review of Amendment STN 125555/0/32
The following review questions were communicated to the sponsor on April 13, 2015. On April 17, 2015, CBER received a partial response from the sponsor in Amendment STN 125555/0/32. A summary of my review questions (in *Italics*), Octapharma's responses (in regular text) and my comments (in **bold**) are below:

1. *The initial BLA submission provided partial equipment clean hold time data. Please clarify if all the production equipment has defined clean hold times.*

Firm's Response
The defined clean hold time for production equipment in contact with product is listed below.

(b) (4)

(b) (4)

The (b) (4) and systems have no defined clean hold time since they are (b) (4)

The freeze dryer has no defined clean hold time since the sterilization of the freeze dryer is performed (b) (4) and the risk for bioburden is very low due to the (b) (4) environment. The freeze dryer has a defined (b) (4) .

Reviewer's Comments
This response is acceptable.

2. *Octapharma should set tighter equipment cleaning acceptance criteria for downstream equipment as an amendment response. The equipment cleaning acceptance criteria for* (b) (4) *do not reflect the process capabilities; i.e., manual cleaning of equipment used for sterile filtration and filling has a* (b) (4) *acceptance criterion of* (b) (4) *and the results are reflecting close to WFI specification at* (b) (4) *at* (b) (4)*. [A correction was sent on April 24, 2015 to state the WFI specification should be* (b) (4)

Firm's Response
The acceptance criteria for (b) (4) will be tightened to reflect the process capability for manual cleaning of equipment used for sterile filtration and filling. Based on the results of the cleaning validation and monitoring data it became evident that a limit for (b) (4) will be more relevant and will reflect the process capability for manual cleaning. A change control will be issued.

The acceptance criterion for (b) (4) will not be tightened due to influence of the surrounding condition in the rooms (b) (4) during sampling on the (b) (4) results. The acceptance criterion of (b) (4) for manual cleaning is considered to be relevant and reflects the process capability for manual cleaning with results from cleaning validation at (b) (4)

Reviewer's Comments
The response is not acceptable. The reported (b) (4) acceptance criteria at (b) (4) and results reported at (b) (4) appear too high for downstream equipment. An additional information request was sent to Octapharma on April 24, 2015 (please refer to IR Question 3). Octapharma has agreed to tighten the sterile filtration and filling equipment cleaning limits for the (b) (4) to reflect WFI at (b) (4) and (b) (4) to reflect WFI at (b) (4) based on Amendment 38 received on April 29, 2015.

3. Please clarify why the (b) (4) control limits were not evaluated as a (b) (4) cleaning metric.

Firm's Response
The current (b) (4) method is presented in Tables 1-5, for (b) (4) used for purification of Antihemophilic Factor (Recombinant) in (b) (4). Each cleaning method is developed for each (b) (4) based on the function of the resin.

The final step of the cleaning and regeneration cycle of the majority of (b) (4) is performed with solution containing (b) (4) which is not suitable for cleaning sampling. Due to this reason, the cleaning sample is performed (b) (4) of the (b) (4).

The (b) (4) is presented in Tables 6-10.
Samples from the (b) (4) passing through the (b) (4) (the (b) (4)) are taken out for (b) (4) analysis.

(b) (4) are not evaluated as a (b) (4) metric since the (b) (4) which is used for cleaning sampling has a high (b) (4) levels and contains (b) (4). Therefore it is not possible to set acceptance criteria for (b) (4).

1 page determined to be not releasable: (b)(4)”

(b) (4)

(b) (4)

(b) (4)

Reviewer's Comments
This response is acceptable.

4. Clarify if the placebo and/or product vials were temperature mapped during the minimum and maximum loads for lyophilizer (b) (4)*. If Octapharma used placebo in place of product for temperature mapping, please provide your rationale and data to support the use of placebo in place of product.*

Firm's Response
The Product temperature was measured in placebo vials based on validation report OC14-0097, which discusses that the product temperature was mapped for (b) (4) positions on each loaded shelf for both minimum and maximum loads.

The freeze-drying process in freeze dryer (b) (4) has been validated using both product and placebo vials based on validation report 30-1684-R04. The table below shows the composition of the product and placebo solution.

Composition of product and placebo solution, placebo solution has the same composition except factor VIII protein

Ingredient	Purpose	Concentration in product/placebo solution (mg/mL)
Sodium chloride* Sucrose* Arginine hydrochloride* Calcium chloride dihydrate* Poloxamer 188* Sodium citrate dehydrate*	(b) (4)	(b) (4)
Factor VIII protein (only in product solution)	*Active ingredient*	(b) (4) *(250 IU)* *(500 IU)* *(1000 IU)* *(2000 IU)*

* Ingredients in the placebo solution

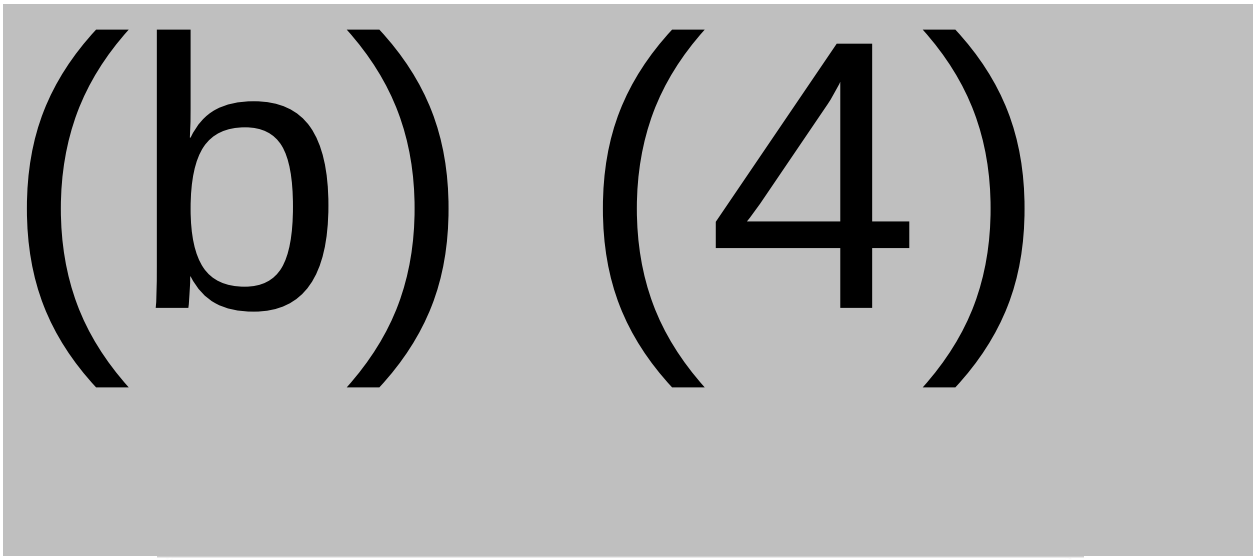
The very low protein concentration in product solution has been assessed not to affect the product temperature measurements based on the product temperature figure shown at the end of this response. The highest protein concentration, for the highest product strength 2000 IU/vial, has been measure to (b) (4) . The excipients have a total concentration in the solution of approximately (b) (4) . Thus the maximum protein concentration in the product solution corresponds to approximately (b) (4) of the total dry substance (b) (4)

The freeze-drying process was validated in validation based on report 30-1684-R04. No product temperature measurements were performed during this validation. For three of the validation batches, both placebo and product vials were evaluated based on the physiological characteristics of the product, i.e. residual moisture, solubility and appearance of the freeze-dried cake. The sampling positions are shown below; product vials were samples on (b) (4) positions and placebo vials were samples on (b) (4) positions on each loaded shelf.

Sampling positions of product vials and placebo vials

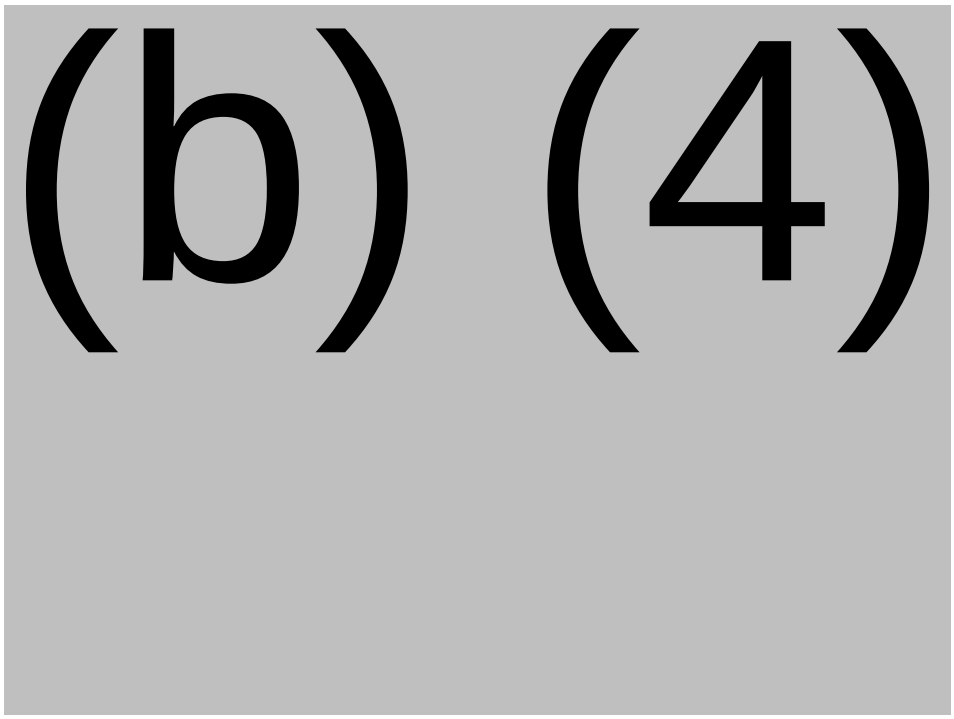
(b) (4)

Results from this validation demonstrated that the freeze-drying characteristics for the placebo and product vials are equivalent, no difference can be seen regarding water content, solubility or appearance of the freeze-dried cakes.



Thus, the placebo and product vials are considered to be equivalent for evaluation of the freeze-drying process. The product temperature measurements performed in the placebo vials are considered representative for the product vials due to the very low protein concentration in the product solution, i.e. maximum (b) (4) of the dry substance concentration. In addition, the comparison of the product characteristics measured for both product and placebo vials ensure equivalent behavior.

The equivalence of the temperature profile for placebo and product solution has been demonstrated for a plasma derived factor VIII product. The protein concentration in the plasma derived factor VIII production solution is approximately (b) (4) compared to the protein concentration of Nuwiq solution which is maximum (b) (4). A high protein concentration is worst-case regarding the equivalence of product temperatures measured in placebo solution compared to product solution. A study was conducted in a developmental scale freeze-dryer (b) (4) with the aim of comparing product temperatures for the plasma derived factor VIII product solution with the corresponding placebo solution. (b) (4) plasma derived factor VIII product solution vials and (b) (4) corresponding placebo solution vials were tested. (b) (4) thermocouples were positioned into product and placebo vials respectively and the temperatures were recorded using data loggers. The freeze-drying chart, including the product temperatures measured in product and placebo vials is described in the figure below.



The product temperatures shown in the figure above verifies that the product temperatures at all steps of the freeze-drying process are comparable for product and placebo solutions. Some minor variations in the time of the initial temperature increase after the finalized sublimation phase can be observed, which is explained by the different vial positions on the shelf and are not related to the product or placebo solutions. This study verifies the placebo and product solution temperature measurements are equivalent during freeze-drying.

Reviewer's Comments

This response appears acceptable. The validation data demonstrated that the freeze-drying characteristics for the placebo and product vials are equivalent regarding water content, solubility and appearance of the freeze-dried cakes. The placebo and product solution temperatures during the freeze-drying process also appear comparable.

5. *Please clarify if the collapse cake temperature for the product* (b) (4) *at all four concentrations is the same. If they are not the same, please provide the collapse cake temperature for each concentration.*

Firm's Response

The collapse cake temperature was determined by freeze-drying microscope measurements for the formulation, i.e. the excipients in their correct concentrations (placebo solution), without Factor VIII protein. The collapse cake temperature for the formulation was measured to be approximately (b) (4).

The excipient concentrations (mg/mL), the fill volume, the product vial and the freeze-drying process are the same for all four product strengths. The protein concentration in the product

solution has been assessed not to affect the collapse cake temperature for the formulation since the protein concentration is very low. The highest protein concentration, for the highest product strength (2000 IU/vial), was measure during the process validation to be (b) (4) . The excipients have a total concentration in the solution to be freeze-dried at approximately (b) (4) . Thus the maximum protein concentration in the product solution corresponds to approximately (b) (4) of the total dry substance. Thus, the collapse cake temperature for the different product strengths are considered to be equivalent based on the very low protein concentration, i.e. maximum (b) (4) of the dry substance concentration in the solution.

Reviewer's Comments
This response appears acceptable.

Review of Amendment STN 125555/0/38
The following review questions were communicated to the sponsor on April 23 and 24, 2015. On April 29, 2015, CBER received a response from the sponsor in Amendment STN 125555/0/38. A summary of my review questions (in *Italics*), Octapharma's responses (in regular text) and my comments (in bold) are below:

1. *Regarding shipping validation,*

a. *Please confirm the summer and winter shipping validations studies address both the 8mL Antihemophilic Factor (Recombinant) vial and the 3mL diluent container.*

Firm's Response
a) Shipping validation study OC13-0363 address shipping of final container 8ml Antihemophilic Factor (Recombinant) vial from Octapharma AB, Stockholm to Octapharma (b) (4) for final packaging. The study does not include the 3 mL diluent container. The 3mL diluent container is produced at (b) (4) and is therefore shipped separately to Octapharma (b) (4) . The shipping validation of the 3 mL diluents container from (b) (4) is currently ongoing.

Reviewer's Comments
This response is acceptable based on feedback from DMPQ management. There is an ongoing shipping validation study for the 3 mL water-for-injection (WFI) diluent container and Octapharma confirmed that they will complete this shipping study. I recommend that this shipping study be reviewed as an inspection follow-up item post licensure to confirm the shipping validation of the 3 mL diluent container from (b) (4) is appropriate. This inspection follow-up recommendation was discussed with Octapharma during a teleconference on May 13, 2015.

b. *Confirm the 8 mL Antihemophilic Factor (Recombinant) and 3 mL diluent vial are shipped together as the final package; if not, please provide a summary of the diluent shipping validation.*

Firm's Response
b) Antihemophilic Factor (Recombinant) vial and the 3mL diluent container will be packed together at Octapharma (b) (4) and shipped together as final package. Shipping Validation of the final package will be performed when shipping the first 3 commercial batches to US (please refer to response 1d).

Reviewer's Comments
This response is acceptable. Octapharma confirmed that they will complete shipping studies of the final product presentation to include air freight transportation to the US. I recommend that the final shipping study data be reviewed as an inspection follow-up item post licensure. This inspection follow-up recommendation was discussed with Octapharma during a teleconference on May 13, 2015.

c. *We noted that you did not include the 8 mL Antihemophilic Factor (Recombinant) vial in your winter shipping validation. Please provide a justification why this is acceptable since it appears like the 8mL vial could be a worst-case scenario.*

Firm's Response
c) Shipping validation study OC13-0363 addresses shipping of final container 8 ml Antihemophilic Factor (Recombinant) vial from Octapharma AB Stockholm to Octapharma (b) (4) during summer seasons.

In course of transport validations during winter season between Octapharma Stockholm, Sweden and Octapharma (b) (4) filled in (b) (4) vials was chosen to be representative for Antihemophilic Factor (Recombinant) filled in 8 mL vials, since both products are packed in identical packaging configurations and shipped at the same temperature range (+ 2°C to + 8°C).

Antihemophilic Factor (Recombinant) (8mL vial) and (b) (4) are both packed in Stockholm in identical unit boxes and shipment boxes (b) (4) The difference in vial size is not considered to influence the temperature distribution since the total mass of the load is comparable.

Therefore the transport validation during winter season including (b) (4) covered by Qualification 080RPQ12019.000 "Transport of final containers (2-8/2-25°C) from (b) (4) and Stockholm, Sweden to (b) (4) Routine Transport-Winter", February 2012 is also valid for Antihemophilic Factor (Recombinant) vials.

Reviewer's Comments
This response is acceptable.

d. *The shipping validation data provided appears to only be performed by truck. Please clarify if you utilize other forms of transportation to your distribution centers to the US, such as plane or ships. If so, please provide shipping validation for the other forms of transportation.*

Firm's Response
c) The shipment of the 8mL Antihemophilic Factor (Recombinant) vials from Octapharma Stockholm, Sweden to the packaging site Octapharma (b) (4) is performed with temperature controlled trucks as well as the shipment of the 8mL Antihemophilic Factor (Recombinant) vials together with the 3 mL diluent container from Octapharma (b) (4), (b) (4) airport. At the airport the 8 mL Antihemophilic Factor (Recombinant) vials together with the 3 mL diluent containers are placed in temperature controlled airfreight containers for the air transport to the United States.

The shipping validation of the complete transport, including the transport in air freight containers, will be performed with the first 3 commercial batches shipped to the United States.

Reviewer's Comments
This response is acceptable based on DMPQ management feedback. Octapharma confirmed that they will complete shipping studies of the final product presentation to include air freight transportation to the US. I recommend that the final shipping study data be reviewed as an inspection follow-up item post licensure. This inspection follow-up recommendation was discussed with Octapharma during a teleconference on May 13, 2015.

2. *Regarding CCIT for the 3mL diluent syringe discussed in Amendment 5,*

a. *Please clarify* (b) (4) *test method.*

Firm's Response
a) (b) (4)

Reviewer's Comments
This response is acceptable.

b. *Please provide evidence that the operators can* (b) (4) *that approaches a critical leak; typically the level of* (b) (4) *is measured by* (b) (4)

Firm's Response
b) A general concentration study was performed to find the detection limit (b) (4) A final concentration of (b) (4) was distinguished from all three lab

assistants. This would mean that (b) (4)

All operators have to pass this initial qualification by using a test set of syringes (b) (4) In addition, operators have to undergo a (b) (4) re-qualification with the test set and a (b) (4) test.

Reviewer's Comments
This response appears acceptable.

c. *We note that you used tested* (b) (4) *tubes with various* (b) (4) *. Beginning at a* (b) (4) *, the tested samples showed a reproducible obvious* (b) (4) *. Please clarify how the limit of detection using* (b) (4) *correlates to the use of a less than or equal to* (b) (4) *positive control for the 3 mL diluent container to ensure appropriate test method sensitivity.*

Firm's Response
a) The serial dilution of the (b) (4) solution was performed to determine the lower visual detection limit for the qualification of the operators.

This visual limit of detection and the limit of detection of the (b) (4) of the test procedure are not linked.

The positive control is a test unit furnished with a (b) (4) tested in parallel with the samples. (b) (4)
For the testing of container closure integrity a (b) (4) is used.
(b) (4) in
length were tested. The prepared syringes were (b) (4) for sample testing:

(b) (4)

Afterwards the syringes were (b) (4) .

(b) (4) Therefore it is regarded as the lower detection limit.

(b) (4)

Reviewer's Comments
This response appears acceptable.

d. *Please clarify if the diluent manufactured at* (b) (4) *is already approved for other US products. If so, please indicate how much of a history you have with this syringe diluent presentation.*

Firm's Response
d) The diluent manufactured at (b) (4) is not approved for any other Octapharma product in the US. However, according to information provided by (b) (4) there are two products approved with the same 3 mL diluents syringe in the US.

Reviewer's Comments
This response is acceptable. The limit of detection for CCIT appears acceptable using a (b) (4)

3. *Regarding sterile filtration and filling equipment cleaning acceptance criteria,*

a. *The information request regarding the WFI specification in Amendment 32 is incorrect. The WFI specification should reflect* (b) (4) *and not* (b) (4) *Please confirm Octapharma can tighten the sterile filtration and filling equipment cleaning limit to reflect WFI at* (b) (4)

Firm's Response
a) The acceptance criteria for the (b) (4) will be tightened to (b) (4) for manual cleaning of equipment used for sterile filtration and filling.

Reviewer's Comments
This response is acceptable.

b. *Please confirm that the* (b) (4) *for the sterile filtration and filling cleaning equipment can reflect WFI at* (b) (4). *The reported* (b) (4) *acceptance criteria at* (b) (4) *and results reported at* (b) (4) *appear too high.*

Firm's Response
b) The acceptance criteria for (b) (4) will be tightened to (b) (4) for manual cleaning of equipment used for sterile filtration and filling.

Reviewer's Comments
This response is acceptable.

c. *Regarding the sterile filtration and filling equipment cleaning, you state that the acceptance criterion for* (b) (4) *will not be tightened due to influence of the surrounding condition in the rooms* (b) (4) *during sampling on the* (b) (4) *results. Please clarify where the* (b) (4) *. Furthermore, please explain how you can assess if the high* (b) (4) *results are from the* (b) (4) *or residues on the equipment. Please note that* (b) (4) *criterion for cleaning for filling equipment should reflect WFI specifications* (b) (4)

Firm's Response
c) The sterile filtration and filling equipment were sampled in the same room as the equipment that was manually cleaned, in (b) (4) The (b) (4) are coming from routine sanitation of gloves and surfaces.

The assessment is that high (b) (4) results come from (b) (4) due to the following reasons:

- (b) (4) .
- (b) (4) .

Reviewer's Comments
This response is acceptable.

Review of Amendment STN 125555/0/39
The following review questions were communicated to the sponsor on April 29, 2015. On April 30, 2015, CBER received a response from the sponsor in Amendment STN 125555/0/39. A summary of my review questions (in *Italics*), Octapharma's responses (in regular text) and my comments (in bold) are below:

1. *Regarding freeze dryer* (b) (4)

a. *Please confirm the defined minimum and maximum number vials that will be processed in the* (b) (4) *freeze dryer. The submission states one batch of DP is defined as* (b) (4) *vials; however this range may not be appropriate since the* (b) (4) *freeze dryer will*

not be used for US production and the process validation data provided for the (b) (4) freeze dryer ranged from (b) (4) vials.

Firm's Response
Octapharma confirmed that the batch size in (b) (4) vials, as described in process validation report 30-1684-R02. Since (b) (4) has been excluded, on batch of Nuwiq will be defined as (b) (4) vials. The batch size will be updated in the MOP and the affected batch records accordingly.

Reviewer's Comments
This response is acceptable.

b. *If the minimum load remains at (b) (4) vials, please provide additional sampling data that can support the use of (b) (4) vials in the (b) (4) freeze dryer. For example, please clarify if the placebo minimum load used for your product temperature mapping study (b) (4) vials) was sampled and evaluated.*

Firm's Response
Not applicable since the minimum batch size in (b) (4) vials.

Reviewer's Comments
This response is acceptable.

c. *Please clarify if you performed any additional (b) (4) minimum loads that could support your minimum load size of (b) (4) vials.*

Firm's Response
Not applicable since the minimum batch size in (b) (4) vials

Reviewer's Comments
This response is acceptable.

Review of Amendment STN 125555/0/42

The following review questions were communicated to the sponsor on April 30, 2015. On May 6, 2015, CBER received a response from the sponsor in Amendment STN 125555/0/42. A summary of my review questions (in *Italics*), Octapharma's responses (in regular text) and my comments (in bold) are below:

1. *Regarding the Octapharma Stockholm and* (b) (4) *visual inspection activities,*

Octapharma Stockholm

a) Please clarify if the Octapharma Stockholm facility is the only location where primary manual visual inspection is performed for the final drug product.

Firm's Response

Octapharma Stockholm is the only location where primary manual visual inspection for Nuwiq is performed.

Reviewer's Comments

This response is acceptable.

b) Please provide a summary of the primary manual visual inspection SOP that includes a description of the defects evaluated by operators and the acceptance criteria used for Nuwiq production.

Firm's Response

The visual inspection is performed as a 100% manual visual inspection by certified operators. The visual inspection is performed to sort out all vials having cap, stopper, glass or content defects. The manual visual inspection of each vial is performed as described below:

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

The vials are (b) (4) during the visual inspection. All defects found during the visual inspection are sorted out and rejected according to the list below:

(b) (4)

(b) (4)

Acceptance criteria

(b) (4)

Reviewer's Comments

This response is acceptable.

c) Clarify how the operators are qualified to perform the primary manual visual inspection to evaluate Nuwiq vial defects.

Firm's Response

All operators must be certified for visual inspection in order to inspect Nuwiq product. The operator is trained by a certified supervisor. The training includes both theoretical and practical training. During the theoretical training all the defects are explained according to the SOP 6019-OFIP "Manual vision inspection of freeze-dryer products," version 11, effective August 29, 2014. During the practical training the operator takes part in the visual inspection under supervision of the supervisor. The supervisor evaluates when the operator is ready for certification. The certification takes place under the same conditions as for normal visual inspection. The operator performs the test independently under supervision by the Quality Unit.

The test material consists of (b) (4) vials have defects and (b) (4) are approved. Among the vials with defects, the three classifications (critical, major and minor defects) must be represented.

During the certification all critical defects should be found and sorted out. At least (b) (4) of major defects should be found and sorted out and at least (b) (4) of the minor defects should be found and sorted out. Of the total number rejected vials there must not be more than (b) (4) approved vials. If the operator does not pass the test, the supervisor should ensure that the operator gets more training, and then repeats the certification but not more than (b) (4) times. The operator for visual inspection has to be re-certified (b) (4).

Reviewer's Comments

Octapharma's manual visual inspection training practice does not appear robust. The number of vials inspected by an operator during training should reflect routine production operations. The (b) (4) freeze-dryer will produce (b) (4) vials. Therefore, operators should be qualified based on the number of vials that is more reflective of routine operations. In addition, one third of the current test kit contains vial defects. The amount of defects evaluated during the operator qualification should reflect what the operator would see in routine production. Typically less than five percent of the vials should have a defect in a routine production run. A teleconference with Octapharma was performed on May 13, 2015 to discuss these concerns and the firm was advised to improve their training program for visual inspection. I recommend that the manual visual inspection training procedure and qualification program be reviewed as an inspection follow-up item post licensure to confirm the firm has improved their manual visual training and qualification program to reflect routine production operations.

Octapharma (b) (4)

d) *Please provide a description of the automatic/semi-automatic (b) (4) line that will be used for Nuwiq production.*

Firm's Response

Visual inspection in (b) (4) covers transport damages including damages on the glass or closure. The (b) (4) is a semi-automatic visual inspection machine (b) (4)

Reviewer's Comments

This response is acceptable.

e) Please clarify that the Octapharma (b) (4) *site only performs a secondary visual inspection using the* (b) (4) *to check for vial defects that may have occurred during the vial transportation from the Stockholm facility.*

Firm's Response
Octapharma (b) (4) only performs a secondary visual inspection using the (b) (4) to check for vial defects that may have occurred during the vial transportation from the Stockholm facility.

Reviewer's Comments
This response is acceptable.

f) Please clarify how operators are qualified to perform the manual visual inspection using the (b) (4) .

Firm's Response
The operators have to pass an initial training and an (b) (4) verification. Furthermore they have to undergo an (b) (4) medical eye investigation.

Initial training - Theoretical part
The employees are instructed on the relevant SOP and on the semi-automatic inspection utilizing the (b) (4) . Possible defects are explained by pictures (defect library) and by examples of defective vials (training and test kits). The training kits consist of vials with various defects (vials with glass and closure defect). Furthermore, criteria for sorting out defect vials and possible types of defects are explained.

Practical part - Training runs

I. The employee gets an instruction how to operate the (b) (4) machine, such as (b) (4) correct viewing technique and discharging of defect vials.
II. The employee then has to perform training at the (b) (4) machine by using test kits under the supervision of an authorized employee. The training is performed with the same machine speeds utilized during routine inspection.

Test runs
Once the employee has performed sufficient training runs, test runs can be started. The test run is again performed with a test kit using the same machine speed as for routine inspection. The vials of the test kit are placed on the intake turntable of the (b) (4) without sorting criterion. Defect vials sorted out during inspection are then sorted according to their inkjet numbers and consecutive numbers, counted and the result is documented. The qualitative check of the sorted out vials is then performed by an authorized person and checked and signed by the head of production.

The test run for the visual inspection for transport damages is passed if the following requirements are fulfilled:

- (b) (4)
- (b) (4)
- (b) (4)

Independently from the above mentioned requirements all critical defects must be found during the test run. The test run may be repeated not more than (b) (4) times. When the (b) (4) test run is not passed the employee will not be qualified for the visual inspection at the Seidenader machine. If an employee failed a test run, the head of production or an authorized person has to perform a re-training session with focus on the overlooked defects.

(b) (4) verification of the visual inspector qualification

The performance of the visual inspection staff is checked (b) (4) by test runs. The (b) (4) verification for visual inspection of transport damage for lyophilized products is performed using one test kit of a lyophilized product. Test kits for product groups are changed (b) (4) . The (b) (4) verification is documented. If an employee failed a test run the head of production or an authorized person has to perform a re-training session with focus on the overlooked defects.

Reviewer's Comments

The secondary visual inspection procedure appears acceptable. During a teleconference on May 13, 2015, Octapharma was asked to ensure their manual visual inspection training procedures reflect routine production operations.

g) Please clarify how many process validation batches have been performed using (b) (4) for Nuwiq production and provide a summary of the acceptance criteria and results.

Firm's Response

Octapharma states the IQ/OQ was successfully completed on January 17, 2012. The acceptance criteria for the IQ were set to check if the components of the machine and the installation are in compliance with the requirements set by the manufacturer. For the OQ/PQ, the acceptance criteria were defined to check the proper operation of the machine.

The following tests were performed for (b) (4)

Standard IQ/OQ-tests

Test	Acceptance Criteria	Result	Deviation
Control of criteria for start of qualification	(b) (4)	Pass	None
Control of internal documentation	(b) (4)	Pass	None
Training	Personnel must have been trained	Pass	None

EIQ (Equipment Installation Qualification) – at (b) (4)

Test	Acceptance Criteria	Result	Deviation
Components of the machine	(b) (4)	Pass	None
Documentation	(b) (4)	Pass	None

EIQ (Equipment Installation Qualification) – at Octapharma

Test	Acceptance Criteria	Result	Deviation
Electrical connection, compressed air supply	(b) (4)	Pass	None
	(b) (4)	Pass	None
	(b) (4)	Pass	None
Wiring diagram and layout	(b) (4)	Pass	None
	(b) (4)	Pass	None
	(b) (4)	Pass	None

CIQ (Computer Installation Qualification) - at (b) (4)

Test	Acceptance Criteria	Result	Deviation
Hardware components	(b) (4)	Pass	None
Hardware configuration	(b) (4)	Pass	None
Software configurations	(b) (4)	Pass	None

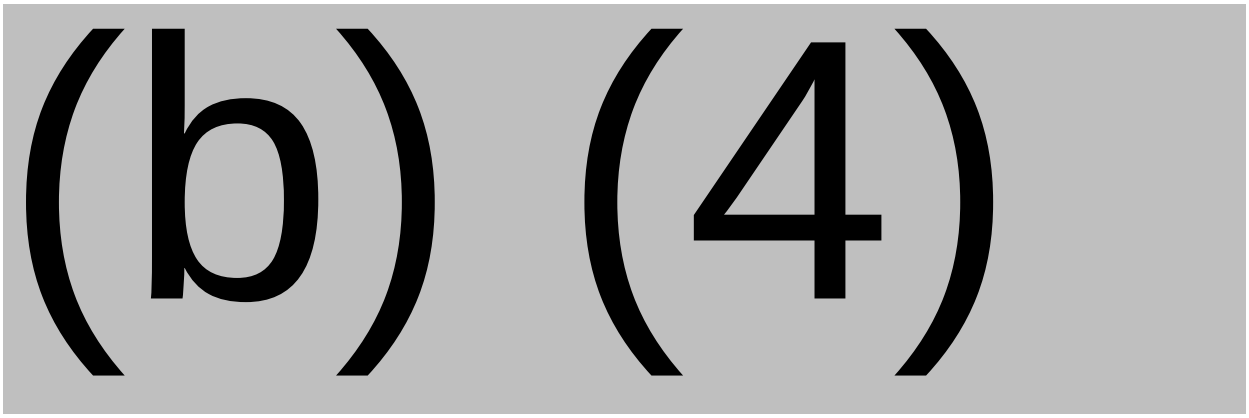
CIQ (Computer Installation Qualification) - at Octapharma

Test	Acceptance Criteria	Result	Deviation
Inputs / outputs	(b) (4)	Pass	None

For the qualification of the (b) (4) machine, 8 mL test vials (filled with water) were used (no validation batches). The vials were processed at the machine for at least (b) (4) The operator tester controls the whole machine and confirms the correct performance in the section "result." The following tables describe the OQ and PQ for the (b) (4) machine.

2 page(s) determined to be not releasable: (b)(4)”

(b) (4)



Reviewer's Comments
This response is acceptable.

h) Please confirm if Packaging (b) (4) *will be the only packaging line used for Nuwiq production.*

Firm's Response
Octapharma clarified that only the packaging (b) (4) will be used for visual inspection for transport damages inspection and labeling of Nuwiq.

Reviewer's Comments
This response is acceptable.